NICOTINE AND THE SMOKING HABIT

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I. INTRODUCTION

Smoking has been indicted by health authorities around the world as a practice which impairs health and shortens life. According to epidemiologists, smoking causes ill health and premature death through coronary heart disease, lung cancer, chronic bronchitis, emphysema and cancers of the upper respiratory tract and even if it does not always cause death or disablement, there is hypermorbidity for these diseases among smokers. Joseph Califano, former Secretary of the US Department of Health, Education and Welfare described smoking as "Preventable Public Health Enemy Number One" which has been convicted, "beyond reasonable doubt, of crimes against the public health" (Califano, 1980).

In this climate of political and medical opinion, it is not surprising that researchers are reluctant to state publicly that smoking can be beneficial in any way, and yet common sense argues that it must be. Smokers are exposed to considerable publicity about the health risks and so every smoker must have made some judgement about the additional risk to health of continuing to smoke. Since cigarettes continue to be purchased, we can only conclude that smokers consider that the risks are outweighed by smoking's benefits.

This belief of smokers about the beneficial effects of smoking is substantiated by this selective but balanced review of the literature on nicotine and the smoking habit. It shows that most smokers absorb nicotine into their bloodstream during the act of cigarette smoking. The nicotine acts on the peripheral nervous system, releasing hormones which reduce fatigue and on the central nervous system to provide more efficient processing of information. This efficiency of function, after nicotine intake, enables people (smokers and non-smokers) to perform better in work situations. In addition, nicotine has a sedative action reducing anxiety and anger. Smokers titrate their nicotine intake according to their view of the situation so that they obtain the appropriate dose of nicotine for stimulation or sedation. In this way, nicotine helps them cope with situational demands, and improves the quality of their lives.

The pharmacokinetic properties of nicotine make smoking doses remarkably safe for normal healthy adults in comparison with other stimulant and sedative substances. Consequently there is a high benefit-risk ratio for nicotine versus other comparable agents. In my view, the unique pharmacological properties of nicotine make it an ideal substance for self-medication by inhalation if the smoke can be made less dangerous. It follows that the less hazardous cigarette will not be a product with low tar, low carbon monoxide and low nicotine but one with the reduction of some smoke constituents but sufficient nicotine (and commensurate taste) to satisfy the smoker, and so prevent more intensive smoking. This type of product would provide the benefits of smoking with minimum risk.

The idea is not new; on the contrary, it was proposed almost 10 years ago (Russell, Wilson, Patel, Cole and Feyerabend, 1973). However, at that time, neither technology nor prevalent thinking was ready for such innovation. Tar and nicotine league tables had only just been introduced, and the limitations of low delivery cigarettes were not yet apparent. Indeed, it is uncertain that all factions would accept such counsel even now. Current opinion is to reduce tar and nicotine conjointly, but such 'across-the-board' reduction in smoke delivery ignores the smoker's needs.

Examination of the evidence (US Surgeon General, 1979 & 1981) suggests that any health problems that may be associated with smoking are more likely to be related to the vehicle by which nicotine is carried (viz, the tar) than to nicotine itself. A more sensible approach to the less hazardous cigarette is thus to provide the smoker with the level of nicotine required, whilst minimising the uptake of unwanted smoke components. The reduction of many other constituents could be tolerated by smokers as long as sufficient nicotine remains: the continuous removal of nicotine, however, may prove ill-advised.

II. NICOTINE PHARMACOKINETICS

Tobacco leaves have a nicotine content between 0.2% and 5% of the dry weight. In a cigarette there is about 10 to 20 mg of nicotine and 14 to 20% is transferred into the mainstream smoke so a 35 ml puff on a 1.2 mg cigarette will give a mouth level of 150-250 µg of nicotine (Armitage, 1973). Tobacco smoke has about 2000 other compounds in it as a complex mixture of gases, uncondensed compounds and liquid droplets as an aerosol. The pH of the mainstream smoke ranges between 5.5 and 6.2 for flue cured cigarettes and between 6.5 and 8.8 for cigar and pipe smoke. The level of acidity is crucial in determining the site of absorption and the amount of nicotine taken from the aerosol.

A. Absorption

The first requirement for a chemical to produce a biological response is absorption. Nicotine from tobacco smoke is absorbed from the mouth, nose, and lungs and digestive tract and the amount absorbed from most sites depends on the acidity of the total smoke.

1. Oral Absorption

Nicotine base is readily absorbed by the buccal membrane from the particulate phase of smoke but, as the amount of free base depends on pH, the amount of nicotine absorbed orally depends on pH. When the pH is 5.35, about 0.4 per cent of the nicotine is present as the free base, while at pH 8.5 (alkaline), 85 per cent of the nicotine is present as the free base. Beckett and Triggs (1967) found in humans that from 1.2 mg of nicotine base about 6% was taken up at pH 5.5 and 25% at pH 8.5. Animal studies with nicotine solutions have shown that a carotid nicotine level of 100 ng/ml can be achieved at pH 6 in the mouth but this increases to 500 ng/ml at pH 8 (Armitage and Turner, 1970). Unpublished research by Dr M A H Russell and Dr K Wesnes, showed that buccal absorption from alkaline tablets containing 1.5 mg nicotine gave venous levels of 6.0 ng/ml at pH 6 and 10.5 ng/ml at pH 9. From these data it would be expected that very little nicotine

would be absorbed orally from cigarette smoke (pH 5.5 to 6.2), perhaps as little as 30% (Armitage, 1973), although much more is taken up from cigar smoke (pH 6.5 to 8.8). In a bioassay study to compare oral absorption of cigar and cigarette smoke, Armitage and Turner (1970) introduced equal numbers of puffs of cigar smoke at pH 8.5 and of cigarette smoke at pH 5.4 into the mouth of an anaesthetised cat. The cigar smoke produced an increase in blood pressure in the femoral artery but cigarette smoke did not. In the same study the oral uptake of radioactively labelled nicotine was compared at pH 7 and pH 8, there was much more taken up when the pH was 8. Thus oral absorption appears to be important for cigar and pipe smokers but much less significant for cigarette smokers. Consequently, a crucial part of the cigarette smoking habit is the further manipulation of smoke by inhaling and then expelling through the nose and mouth or even just expelling through the nose.

2. Nasal Absorption

In order to account for the habit of snuff taking, which is found in many cultures, and the popularity of snuff taking among smokers working in munitions factories, it has been suggested that nicotine is absorbed by the nasal mucosa (Proosdij, 1960). Evidence for this explanation has come from two studies. Temple (1976) found that snuff taking resulted in measurable levels of nicotine and its major metabolites in urine. More recently, Russell described the time course of plasma nicotine that resulted from snuff taking by an experienced snuff taker (Russell, Jarvis and Feyerabend, 1980). Uptake of nicotine from the nasal mucous membrane was extremely rapid and nicotine concentrations of over 20 ng/ml were found in blood samples from a forearm vein. Therefore, it would seem probable that nicotine is absorbed from the nose during smoke manipulation but the absorbed amount is probably small in comparison with the uptake that results from inhalation.

3. Inhalation

The major site of nicotine absorption for cigarette smoke (and so for the majority of smokers) is the lungs. During inhalation, the smoke

aerosol passes down the bronchi and into the alveoli. Particles of cigarette smoke are an ideal size (0.01 - 2 µm) for penetration into the alveoli and absorption occurs through the thin alveolar membrane into the pulmonary capillaries. It is estimated that more than 90% - 95% of inhaled nicotine is absorbed (Armitage, Dollery, George, Houseman, Lewis and Turner, 1974; Armitage and Turner, 1980; Artho and Grob, 1964). When equivalent sized boli of cigar or cigarette smoke were puffed into a cat's lung, changes in femoral artery blood pressure suggested much more efficient uptake of nicotine from cigarette smoke than cigar smoke (Armitage, Hall and Morrison, 1968). Nicotine diffuses so rapidly across the alveolar membrane and the velocity of blood flow through the capillaries is so slow that equilibrium is probably reached between alveolar nicotine and capillary nicotine ensuring maximum uptake. On the basis of the previous estimates of 150 to 250 µg mouth level of nicotine from each puff, over 100 µg would be taken up during each inhalation from a medium delivery cigarette (Armitage, Houseman, Turner and Wilson, 1974) giving over 1.0 mg of nicotine per cigarette. Of course, the actual intake may not only depend on smoke generation (puffing pattern) and smoke manipulation (quantity inhaled and depth of inhalation) but also perhaps on smoke moisture, pH of mucus membrane, and the contact time with the alveoli.

The time course of nicotine in human plasma has been studied most extensively by Dr M A H Russell. Smokers puffed ten times on a cigarette and plasma samples were taken every five minutes from an indwelling needle in a forearm vein. There was a rapid increase in plasma nicotine with each puff with irregularities in the ascent profile from the puff by puff boluses of nicotine. Peak venous nicotine levels of 15.5 to 38.4 ng/ml were reached at the end of the cigarette and then corresponded to about one fifth or one sixth of the carotid artery levels. Nicotine decay is not smooth either, and Russell (1976) argues that the irregularities represent nicotine redistribution and recycling. The estimated overall half-life in humans is around 20 mins after finishing the cigarette and baseline levels of about 7 ng/ml are reached in 40 mins.

4. Gastric Absorption

Gastric absorption only plays a small part in nicotine uptake from cigarette smoking in normal circumstances. Nicotine from the smoke aerosol will dissolve in the saliva where pH ranges of between 5.6 and 7.6 would give about 6 per cent to 20 per cent free nicotine base. Travell (1967) showed that nicotine was rapidly absorbed from a cat's stomach when the solution pH was between 7.8 and 8.6 but not when the solution was acidic, with a pH between 1.2 and 4.2. There is evidence of active nicotine excretion from the salivary glands. This nicotine passes into the stomach and Russell (1976) has suggested that this "recycled" nicotine could maintain the plasma levels of nicotine in smokers. However this seems unlikely; the normal gastric pH is acidic and so nicotine will be absorbed very little from the stomach although absorption from other regions of the digestive tract cannot be ruled out.

5. Summary

The amazing, complicated practice of puffing on burning tobacco leaves, inhaling the smoke and blowing it out through the nose and mouth has a simple explanation. This procedure enables the most efficient transfer of nicotine from the tobacco leaves to the smoker's bloodstream and more importantly the smoker can control the level of nicotine intake (see Section III).

B. Distribution

After absorption into the pulmonary capillaries, nicotine does not bind to plasma protein and so all the nicotine is available for biological activity. The nicotine-loaded blood leaves the lungs via the pulmonary veins and passes through the left atrium of the heart into the left ventricles. From there the nicotine is pumped out into the aorta from which the large arteries branch off. The significant branch, from the point of view of the smoking habit, is the carotid artery which leads directly to the brain, so that some absorbed nicotine passes directly unmetabolised from lung to brain within 10 secs. About a fifth of the blood from the heart ascends in the carotid artery so that a fifth of the absorbed nicotine passes to the brain (Oldendorf, 1977) ie a dose of around 250 µg from a medium delivery cigarette on the basis of the previous assumptions.

1. Brain

In order to act on the brain, a substance must penetrate the blood-brain barrier (mainly the membrane lipid of the brain capillary walls) to the brain extracellular fluid. Nicotine is soluble in lipid (partition coefficient of 0.4) which suggests that it will freely pass through this barrier. Studies in the rat have compared the percentage of nicotine remaining in the brain 15 seconds after a rapid intracarotid injection with tritiated water as a standard. Ninety per cent of the tritiated water is taken up by the brain on the first pass through the brain, and uptake of nicotine is 131% that of tritiated water. (Oldendorf, Hyman, Brown and Oldendorf, 1972). Thus virtually all the nicotine that is delivered to the brain leaves the blood since the volume of brain tissue to which it can distributed is so much larger than the capillary plasma volume. As a result, the amount of nicotine entering the brain is proportional to the cardiac output to the brain ie about 250 µg nicotine per cigarette. As a consequence of this efficient uptake of nicotine, doses affecting the brain can be obtained with relatively low blood levels which minimises the risk of toxicity to other organs in the body.

Whole body autoradiograms of mice given intravenous doses of ^{14}C-nicotine reveal a high accumulation of nicotine in the grey matter (unmyelinated tissue) with much smaller quantities in the white matter. This distribution occurs because nicotine's partition coefficient of 0.4 allows good penetration of the blood-brain barrier but does not result in depot fat storage. Microautoradiograms after ^{14}C-nicotine and ^{3}H-nicotine show radioactivity in cortical cells, high levels in molecular and pyramidal cells of the hippocampus, the molecular layer of the cerebellum, the nuclei of the hypothalamus and the brain stem (Schmiterlöw, Hanson, Applegren and Hoffman, 1967). This pattern of nicotine distribution throughout the brain allows wide scope for pharmacodynamic interaction.

The time course of nicotine distribution in mouse brain shows that the maximum concentration is reached within one minute of an intravenous injection. The level then decreases rapidly to about 50 per cent in five minutes and one per cent after an hour (Stalhandske, 1970). Similarly Schmiterlöw found a rapid nicotine decrease from 3.93 µg (per gram of brain tissue) at five minutes to 0.71 µg at 20 minutes and 0.10 µg at one hour (Schmiterlöw, Hanson and Andersson, 1967). As these workers and others found, the brain does not metabolize nicotine but the drug washes out quickly from the brain and so gives a short duration of action. Thus nicotine is a drug which is rapidly absorbed into the brain, widely distributed and then quickly removed; the ideal specifications for a substance that is required for a short duration of action.

2. Rest of the Body

The nicotine that is eliminated from the brain is redistributed around the rest of the body and joins the nicotine introduced via the other arteries from the aorta. As the partition coefficient is less than one very little storage in solution in fatty tissues results. Instead, whole body autoradiograms (Schmiterlöw et al 1967) show a pattern of distribution after intravenous injection that corresponds to the blood supply, with the highest levels of radioactivity in the liver (4% of the injected dose), about the same levels in the kidneys as in the brain (2% of the injected dose) and less in the stomach.

In contrast to the brain, nicotine is metabolised in the liver and kidneys (see next section) and nicotine levels in the liver fall from 8.12 µg (per gram of tissue) at five minutes to 0.76 µg at 20 minutes ie about 90% is metabolised in 15 minutes. At 20 minutes the radioactivity in the liver and kidneys is mainly due to cotinine and other metabolites of nicotine (Schmiterlöw et al 1967).

C. Metabolism and Excretion

Metabolism and excretion have been discussed at length in numerous publications. However there are two aspects of major importance to the smoking habit. First, it is clear from the time course that nicotine

is metabolised very efficiently by the liver, this limits nicotine's duration of action in the body. Second, the metabolites appear to be virtually inactive. Metabolic transformation is carried out by the enzyme systems of the liver microsomes and it seems that microsomal oxidation systems are protected by a lipoid barrier (Brodie, Maickel and Jondorf, 1958) which nicotine is fat-soluble enough to penetrate. The major metabolic route is probably hydroxylation (insertion of a carbonyl group in the pyrrolidine ring) to form cotinine. In addition, other metabolites, including nicotine 1-N-oxide and nornicotine, are formed and excreted. The importance of this metabolic outcome is that no compounds of demonstrated pharmacological action are produced and the pharmacodynamic effects are determined almost completely by the action of nicotine alone.

D. Conclusion

Studies of nicotine pharmacokinetics have revealed it to be a substance which is absorbed very efficiently from the lungs, readily enters and is quickly eliminated from the brain, and is rapidly metabolised to relatively inactive metabolites. This pharmacokinetic pattern allows a brief duration of action and the possibility of central nervous action with minimum side effects from actions on the rest of the body. The realization of this possibility depends on the ability of the smoker to control his exposure to nicotine ie titrate for nicotine.

III. NICOTINE CONTROL

The first argument for the relevance of nicotine to the smoking habit comes from evidence that people smoke to obtain nicotine, and many of them appear to regulate nicotine intake to obtain specific levels of nicotine in their bloodstream. The implication of titration is that smokers have need for nicotine and possess a mechanism in the body which is sensitive to nicotine so enabling them to titrate the dose. Evidence for nicotine need and titration has come from surveys of cigarette preference, studies of inhalation, studies of smoking patterns throughout the day, the titration of individual cigarettes, nicotine preloading studies and a nicotine antagonist experiment.

A. Preferred Cigarette Brands

In 1957 the Readers' Digest magazine published a list of the deliveries of nicotine and total particulate matter from cigarette brands in the United States. At that time only one per cent of the cigarettes were filter-type and the average cigarette delivered 2.5 mg of nicotine and around 36 mg of particulte matter. After the adverse publicity in the United States from the Surgeon General's report in 1964, and the reports in 1962 and 1971 of the Royal College of Physicians in Britain, the average levels of nicotine, determined by smoking machine analyses, were 1.3 mg. After 1966, American cigarette manufacturers cited tar and nicotine levels in their advertisements and competition began, between the manufacturers, to introduce lower delivery cigarettes onto the market. In 1977 just under half of the United States cigarette industry's budget for advertising and promotion was used to encourage the purchase of these products (US Public Health Service, 1979), and a similar pattern has occurred in the United Kingdom.

It might have been expected that the combination of government publicity and company promotion would have produced an even more remarkable switch in brands to lower nicotine and tar yields in the following ten years, and the sales-weighted average nicotine per cigarette would have decreased at least a further 1.0 mg to 0.3 mg. In fact, cigarettes with a nicotine

content of 0.3 mg and correspondingly low levels of particular matter are not popular, and the sales-weighted average level of nicotine in UK cigarettes has been 1.3 - 1.4 mg per cigarette for the past 8 years, and in the United States it is only approaching 1.1 mg. In Germany there is a similar pattern and the sales-weighted average of nicotine did drop to 0.6 mg but is now around 0.8 mg. The Germany figure may be lower because the Ph of alkaline so increasing absorption (see Section II A). Nicotine-free cigarettes have been a total disaster, even though many people have tried them. Clearly, smokers not only prefer nicotine-containing cigarettes, but most smokers select brands which give a machine smoking delivery of above 1.0 mg of nicotine.

It could be argued that these observations on cigarette preferences do not provide convincing evidence for the importance of nicotine because nicotine usually co-varies with particulate matter in cigarette brands as a consequence of the manufacturing techniques. However, one controlled study has tested cigarettes with independently varied nicotine and tar levels. (Goldfarb, Jarvik and Glick, 1970). Smokers were allowed to smoke as many as they wished of these cigarettes with varying amounts of nicotine and the number of cigarettes that they smoked correlated with nicotine content but not tar content. Ratings of satisfaction and the perceived strength of the cigarette were similarly correlated with nicotine content rather than tar content. Nevertheless, it is interesting that non-nicotine cigarettes were smoked to some extent over the three weeks of the test when there were no other alternatives.

Although low and zero nicotine cigarettes allow the smoker to go through the rituals of lighting, manipulating, and puffing the cigarette as well as inhaling the smoke, the lack of nicotine results in lower consumption. However, it would be fallacious to conclude that flavour from the particular phase of tobacco smoke plays no part in the acceptability of a cigarette. Nevertheless, the inference from these surveys and studies is that nicotine is an essential ingredient of the cigarette for the smoker and this conclusion becomes even clearer when a more complete measure of smoking behaviour, than number of cigarettes smoked, is used.

D. Nicotine Titration

In this part I will consider the direct evidence for smokers controlling their nicotine intake either by smoking less intensely with higher delivery cigarettes or smoking more intensely with lower delivery brands. For convenience this section will be sub-divided into cigarette consumption, smoke generation and smoke manipulation, and within each sub-section, the methods of study.

1. Cigarette Consumption

The number smoked is the most obvious way for smokers to control their nicotine intake and it is the easiest to study. However, as we shall see, it is not without its problems. For instance, the number of cigarettes in a pack has a strong influence on consumption. The first studies examined the effects of changing the cigarette brand on consumption.

a. Cigarette Switching

The findings of Russell et al (1973; 1975), which strongly hinted that smokers control their nicotine intake were explored further by switching the subjects from their usual brand (1.5 mg average) to both high (3.2 mg) and low (0.3 mg) nicotine cigarettes on different days. The number smoked during the five hours in the middle of the day was recorded. When switched to the high nicotine cigarette, consumption of the group dropped by 37 per cent, from 10.8 $\pm$ 3.5 to 6.7 $\pm$ 1.6, and increased, by 17 per cent, from 10.7 $\pm$ 3.5 to 12.5 $\pm$ 3.2, when they changed from their usual brand to a low nicotine cigarette (average = mean $\pm$ standard deviation). The decrease with the high nicotine delivery cigarette was significant but the increase with the low nicotine delivery cigarette was not. However, in terms of nicotine delivery of the latter product, subjects would have needed to smoke five times as many to compensate (an increase from 10.7 to 53.5) if they did not change other aspects of their smoking behaviour in any way.

B. Inhalation

As discussed in Section II, smoke inhalation results in very efficient absorption of nicotine; the large percentage of smokers who inhale provides evidence that the aim of smoking is to obtain nicotine. Epidemiological studies of smoke-related diseases have surveyed self reported inhalation behaviour (Doll and Hill, 1964; Hammond, 1966). Doll and Hill's study showed that 80 - 90 per cent of cigarette smokers reporting inhaling, and Hammond found that 96.4 per cent of smokers, aged between 40 and 49, said that they inhaled to some extent and 85.6 per cent thought that they were moderate to deep inhalers. Todd (1968; 1971) reported similar data with 9 per cent and 8 per cent of smokers believing that they did not inhale at all and 77 per cent saying that they inahled "a lot" or "a fair amount". The problem with self reported inhalation data is that it may be inaccurate because smokers underestimate the extent to which they inhale (Castleden and Cole, 1973). Therefore the percentage of inhalers is probably higher than these surveys suggest, strengthening the argument that smokers use cigarettes to obtain nicotine.

C. Smoking Pattern

The hypothesis that smokers attempt to maintain minimum (or above) levels of nicotine is supported by studies of plasma levels of nicotine throughout the day (Russell, Wilson, Patel, Cole and Feyerabend, 1973; Russell, Wilson, Patel, Feyerabend and Cole, 1975). The half-life of nicotine in plasma (see Section II) is about 20 to 30 minutes and habitual smokers consumed 15 to 30 cigarettes per day, ie a cigarette every 30 to 50 minutes (excluding meals and sleep). Russell's studies demonstrated that the mid-morning levels of plasma nicotine were remarkably consistent within subjects across days (small standard error), although the levels for individuals ranged from 5.6 to 83.3 ng/ml. A determination five hours later in the afternnon showed that these levels were either virtually the same or higher which again supports the hypothesis that smokers use cigarettes to obtain nicotine.

A large scale interview study which looked at the number smoked has given similar findings for switching to lower yield brands. Waingrow and Horn (1968) interviewed a group of 1466 cigarette smokers in 1964 and again in 1966. They found no evidence that smokers, who switched to lower delivery cigarettes, increased their consumption. However, it was again assumed that the smokers did not change their smoking behaviour to obtain more nicotine. Russell (1976) has also pointed out that there may have been self-selection in the sense that only smokers with a low requirement for nicotine switched brands and so could accept the reduced delivery without feeling deprived.

In a shorter term laboratory study, Frith (1971) gave smokers cigarettes with deliveries of 1.02 mg, 1.37 mg and 2.11 mg of nicotine to smoke on single days. The number of cigarettes that were smoked was recorded throughout the day from 9.00 am to 5.00 pm, and the smokers also rated their desire to smoke before and after each one. An inverse relation was found between the number of cigarettes smoked and the nicotine level. Subjects also said that they found the high delivery cigarette more satisfying than the low delivery. Unfortunately, the tar level of the lowest cigarette was half that of the highest (14.6 against 30.8) and so the subjects could easily detect the differences between the products. In a better two hour experiment, smokers were given specially prepared cigarettes which were either of low nicotine delivery (0.2 mg) or high nicotine delivery (2.0 mg) (Jarvik, Popek, Schneider, Baer-Weiss and Gritz, 1978). The tar levels of the cigarettes were identical so that the taste difference was small. Subjects smoked more of the lower delivery than the higher delivery cigarette which gives persuasive support for nicotine regulation.

Better controlled studies have looked at smoking in real life situations. In the first, smokers were given a medium delivery cigarette for the first week, a low to medium cigarette in the second week, and a low cigarette in the third week (Turner, Sillet and Ball, 1974). The subjects compensated by smoking significantly more cigarettes when they switched from the medium to the low-medium cigarettes, but there was little change after the second switch from low-medium to the low delivery product. A longer study (Freedman and Fletcher, 1976)

examined the changes in consumption over a 20 month period when smokers were switched from a conventional medium (1.39 mg) nicotine cigarette to a lower medium (1.01 mg) cigarette containing 30 per cent tobacco substitute. The average number of cigarettes smoked remained constant for the first 15 months, but increased slightly in the last 5 months. Although consistent with nicotine regulation, this small but significant increase was surprising in view of the similarity of the nicotine yields of the two cigarettes.

The problems of cigarette consumption experiments were highlighted by long term studies by Adams (1976; 1978) of smokers from the Imperial Tobacco Company Research Division and Head Office which will also be referred to later. Two sets of subjects smoked their own brand for a week, then medium nicotine (1.4 mg) cigarettes for five weeks and then a low-medium nicotine (0.8 mg) cigarettes for four weeks. Two control groups smoked their own brand for a week and then either the low cigarette or low-medium cigarette for the remaining nine weeks. The Research Division subjects increased their weekly consumption markedly when switched to the low nicotine product while the Head Office subjects increased their number only slightly. Adams believes that members of the Head Office smoking panel were less familiar with the experimenters and were inhibited in their demands for more free cigarettes. An equivalent psychological barrier may operate in real life where smokers may choose a lower delivery brand but are reluctant to purchase more cigarettes than they usually do.

A methodologically sophisticated long term study was performed by Finnegan, Larson and Haag (1945) using tobacco leaf with naturally low nicotine content made into a low nicotine (0.34 mg) cigarette or the same leaves sprayed with nicotine and made up into a high nicotine (1.96 mg) cigarette. Thus the pressure drop of the cigarettes and the tar level would be the same and, although the nicotine would give a slightly different taste, it was possible to test the effects on consumption without the subjects being certain about the difference. Subjects were given 400 of the high nicotine product followed by a month on the low nicotine brand and then switched back to 400 of the high nicotine cigarette. The authors claimed that there was no

correlation between the number of cigarettes smoked and the nicotine level, a finding which argues against compensation. However, an interesting picture emerged when Russell (1976) examined the distribution of withdrawal symptoms in this study; subjects who did not increase their consumption on the low nicotine cigarette experienced lack of satisfaction, irritability and poorer concentration.

Instead of examining a mixed set of subjects, as in the last study, Schachter (1977) selected an "addicted" group and a "non-addicted" group. The addicted group members had smoked at least 20 cigarettes a day for many years, they smoked regularly throughout the day from morning to night, they inhaled the smoke, they were not trying to stop or cut down at the time of the study, and, if they had tried to abstain, then they had experienced abstinence symptoms. Half the subjects were given low nicotine (0.3 mg) cigarettes for the first week and half were given medium nicotine (1.3 mg) cigarettes for the first week, then they were switched to the other cigarette for the second week. Although the experiment was carried out double blind the cigarettes differed to some extent in tar content. As a group, the addicted smokers smoked 2% per cent more of the low nicotine cigarettes (42.93) than the high nicotine (34.57), while the light smokers used 16 per cent more of the low nicotine (10.19) compared with the high nicotine cigarette (8.81). Schachter reorted that three addicted subjects, who only increased consumption by 14.3 per cent compared with 33.6 per cent for the rest, experienced severe abstinence symptoms. Thus the last two studies show that smokers who do not regulate their nicotine intake, suffer deprivation symptoms.

b. Ventilated Holder

Another method of varying smoke delivery to the smoker is to use a normal cigarette but smoked through a ventilated cigarette holder. Two holders producing nicotine dilutions of 23 per cent and 58 per cent were used to study titration (Sutton, Russell, Feyerabend and Sallojee, 1978). Smokers used each holder for a week and kept a diary of their cigarette consumption. Consumption remained constant

throughout the study and no titration was seen on this measure. However, as we will see later, compensation was achieved by increasing the amount of smoke inhaled.

c. Partial Cigarettes

A third type of study has examined the number smoked when subjects were only allowed to smoke part of a cigarette for a week. Goldfarb and Jarvik (1972) gave smokers packs of cigarettes which were either cut in half or had a line drawn around them halfway down, and the number of smoked cigarettes was counted. In comparison with smoking their own brand in week 1 (25.5), smoking increased with the lined cigarette (27.2) and the cut cigarette (28.6), but during the fourth week on their own brand smoking was also higher (27.3). These group data give limited support for titration by increasing the number smoked because 12 subjects did increase by an average of five a day on the lined cigarettes and by an average of seven a day on the cut cigarettes. A more extensive study (Russell, Sutton, Feyerabend and Cole, 1978) included a full length medium nicotine (1.08 mg) cigarette, a threequarter length, low-medium nicotine (0.83 mg) cigarette and a half length, low medium nicotine (0.67 mg) cigarette. These cigarettes were smoked in the laboratory on three separate afternoons. The number smoked increased from 13.6 with the full length cigarette, 14.8 with the threequarter length and 17.6 with the half length. Thus there was a clear and significant increase in consumption, in contrast to the rather small changes found by Goldfarb and Jarvik.

d. Nicotine Preload

A fourth approach has been to preload the smokers with nicotine, either by injection or oral doses. The pioneer study of this type, and indeed the first study of titration, was done by Johnston (1942). He injected 20 mg of nicotine intravenously and reported that smokers found the sensation pleasant and did not want to smoke for some time afterwards. No details were given of number consumed. In a follow-up study (Lucchesi, Schuster and Emley, 1967), subjects were given intravenous infusions of nicotine and their cigarette consumption examined. Low

doses of nicotine had no effect, but 4 mg per hour very significantly reduced consumption of a cigarette of unspecified delivery by 27 per cent (10 to 7.3). Although significant, this decrease in numbers is small in comparison with the amount of nicotine given, but it must be remembered that nicotine is rapidly metabolised by the liver (see Section II) so that the levels reaching the brain would be much smaller than those infused.

The same problem applies to studies using oral nicotine whether in tablet or chewing gum form so that it is scarcely surprising that a daily dose of five tablets of 1.0 mg of nicotine reduced the number of cigarettes used by only eight per cent although this was a significant decrease (Jarvik, Glick and Nakamura, 1970). Nicotine chewing gum has been prescribed as a stopping-smoking aid, and some success has been claimed. In an experimental study (Russell, Wilson, Feyerabend and Cole, 1976), subjects were given either alkaline gum with nicotine (a high pH increases buccal and gastric absorption; see Section II A.1), or a placebo, both highly spiced so that the subjects could not tell which was which. A plasma nicotine determination showed that nicotine was absorbed from the nicotine gum although blood levels were lower than with smoking. Subjects reduced their smoking on both gums but significantly more so while taking the nicotine gum (37 per cent) than after the non-nicotine gum (31 per cent). Clearly, in spite of a placebo effect, when the subjects thought that they were getting nicotine gum, there was some reduction of consumption.

e. Modified Excretion

A fifth type of study manipulated nicotine body levels by changing urine acidity. If the urine is alkaline then less than one per cent of the nicotine is excreted unchanged in the urine, if it is neutral then seven per cent is excreted and if the urine is acid then 35 per cent is excreted unchanged (Beckett and Triggs, 1967). Presumably an increase in urinary excretion should lower plasma levels of nicotine and so Schachter predicted that increasing acidity should increase smoking. In a test of this prediction (Schachter, Kozlowski and Silverstein, 1977) ascorbic acid (Vitamin C) or glutamic acid

hydrochloride was given to smokers to acidify their urine and increase excretion. There were increases in consumption from 23.1 to 26.7 (15.6 per cent) and 28.1 (21.6 per cent) respectively. Once again there was some evidence for control of nicotine intake by changing consumption.

f. Nicotine Antagonists

A complementary study to those on nicotine loading is one using the secondary amine, mecamylamine, which crosses the blood brain barrier and blocks nicotinic synapses in the central nervous system (Stolerman, Goldfarb, Fink and Jarvik, 1973). Smokers were given this drug or pentolinium, a nicotinic blocker which does not enter the brain, and asked to record the number that they smoked of their usual cigarettes (range 1.0 - 1.5 nicotine). Mecamylamine, (7.5 mg, 12.5 mg, 17.5 mg and 22.5 mg) increased cigarette consumption by as much as 30 per cent, presumably smokers smoked more to overcome the partial nicotine blockade in the brain and so obtain the desired effects of nicotine. When the smokers had taken pentolinium there was no change in the number of cigarettes smoked which ruled out any influence of the peripheral effects of nicotine on consumption. This study shows clearly that smokers are using cigarettes to obtain plasma levels of nicotine sufficient to affect the brain.

g. Summary

These studies show that some subjects titrate nicotine by changing the number of cigarettes that they smoke. In studies where abstinence symptoms have been examined, some smokers, who do not compensate, suffer from the effects of nicotine deprivation. However, negative studies may be explained in terms of changes in either puffing or inhalation. Data, that show these factors play a part, come from an experiment by Gritz, Baer-Weiss and Jarvik (1976) in which subjects were given an equal number of full length cigarettes and half length cigarettes to smoke in a week. Urinary nicotine measures showed that subjects were able to obtain considerably more nicotine than expected

from the half length cigarettes, and indeed almost as much as from the full cigarette. The authors concluded that "frequency of puff, size of puff or depth of inhalation must have altered on the shorter cigarette to maximise nicotine intake and achieve optimal titration". (P.554).

2. Smoke Generation

In the last section, the conclusions on cigarette consumption were related to the nicotine content of the cigarettes. These nicotine levels were calculated on the basis of nicotine deliveries that were obtained from standard smoking machines. The machine smoking determinations enable comparisons of cigarettes, but the smoking machine only produces an approximation of human smoking. The underlying principle of the machine determination of smoke deliveries is that standard analytical procedures are such that the yield is representative of the smoke a cigarette delivers to the smoker if the same smoking parameters are applied. In an innovative series of studies, Creighton and Lewis (1978 a and b) recorded the pattern of smoking in terms of number of puffs, puff interval, puff volume and puff shape. They found that there were marked interindividual differences in smoking pattern and clear, but smaller, intraindividual variations. Therefore it was inevitable that an individual's pattern of generation rarely matched the smoking machine's standard parameters. The consequences of variations in smoking pattern for nicotine deliveries were smaller than those for total particulate matter and carbon monoxide. Nicotine increased markedly with the number of puffs, but there were only small changes for puff interval and puff volume, while puff shape had no effect on nicotine delivery.

The practical consequence of these variations in smoking pattern, in terms of nicotine deliveries, was examined in a complementary study with the puff duplicator (Creighton and Lewis, 1978 a). The divergence of the standard smoking machine yields from the actual values delivered can be seen by comparing the average amount of nicotine that was deposited on the Cambridge filter pad after duplicating the smoking patterns for a medium delivery cigarette having a yield of 1.4 mg of nicotine when analysed on a machine smoking to standard parameters. This was 2.25 mg

of nicotine for males and 2.0 mg of nicotine for females. The coefficient of variation for nicotine deliveries between different subjects who smoked the same brand ranged from 24 per cent to 38 per cent with a mean of around 30 per cent. Clearly the machine estimated delivery is a limited index of the nicotine dose entering a smokers mouth, and so other estimates of nicotine delivered to the mouth should be used.

Some of the previous studies of nicotine regulation recorded puff variables as well as numbers of cigarettes consumed. The experiment of Frith (1971) demonstrated that, as well as smoking more cigarettes, smokers took larger puff volumes for some cigarettes than others. Lucchesi et al (1967) found that intravenous nicotine reduced the number of puffs and the subjects discarded their cigarette earlier. A similar study by Kumar (Kumar, Cooke, Lader and Russell, 1977), however, found no changes in puff number, interpuff interval, puff duration or puff volume on a 1.3 mg cigarette after 10 rapid injections of nicotine; either 0.035 mg/kg or 0.07 mg/kg spaced at one minute intervals in order to simulate 10 puffs on a 0.85 mg or a 1.7 mg cigarette. A companion study, with controlled smoking of either a herbal cigarette, a 1.3 mg nicotine cigarette or two 1.3 mg nicotine cigarettes (ie 2.6 mg) did reduce the number of puffs taken from a cigarette in a dose dependent fashion. The major problem with comparing studies of intravenous and inhaled nicotine is that some of the intravenous nicotine is metabolised before reaching the brain and so the dose is lower than that going from lung to brain. This evidence suggests that smokers can control the nicotine intake to their mouth by changing their smoke generation. Direct studies of this behaviour have employed cigarette switching and partial cigarettes.

a. Cigarette Switching

Estimates of nicotine which is drawn into the smokers mouth have been made from analyses of the nicotine deposited in the cigarette filter and the filtration efficiency of the filter tip. One of the first studies on butt nicotine allowed smokers to smoke either a 1.0 mg or 2.1 mg nicotine cigarette while in a driving simulator (Ashton and Watson, 1970). Records were made of puff number and depth of inhalation while the butts were collected. Depth of inhalation was

unchanged but puff number was large on the medium delivery cigarette and butt nicotine data showed that about the same amount of nicotine was delivered to the mouth from both cigarettes (1.31 mg from the 1.0 mg nicotine cigarette, a ratio of 1.31, and 1.55 from the 2.1 mg nicotine cigarette, a ratio of 0.74). This study gave clear evidence of titration, by smoking the lower delivery cigarette more intensely and puffing the higher delivery product less intensely. In our own studies (Warburton and Wesnes, 1978) we found similar changes during a vigilance test. Smokers smoked both a low nicotine (0.3 mg) delivery cigarette and a low-medium nicotine (0.7 mg) cigarette more intensely and an estimated 0.68 mg and 1.3 mg of nicotine entered the mouth (ratios of 2.28 and 1.85). When they smoked a 1.64 mg nicotine cigarette, slightly less intensely, they obtained an estimated 1.55 mg of nicotine in the mouth (a puffing intensity ratio of 0.94).

In the longer term study by Turner et al (1974) there were differences in the number of cigarettes smoked between a medium nicotine and a low-medium nicotine product but not between the low-medium and a low brand. There was little difference between the medium and low-medium nicotine cigarettes (puffing intensity ratios of 0.62 and 0.77) but subjects puffed the low delivery cigarette more intensely (a puffing intensity ratio of 1.23). Clearly, the same subjects titrated by changing either the number smoked or the smoke generation in order to obtain their desired nicotine level. In the even longer study by Freedman and Fletcher (1976), in which there were only small changes in the numbers smoked when subjects switched from a 1.39 mg nicotine cigarette to a 1.01 mg product, butt nicotine levels also showed more intense smoking of the lower brand in comparison with the higher delivery cigarette. Puffing intensity ratios of 1.06 and 0.81 were found according to a reanalysis of the data by Rawbone (1976). In another long cross-over study, smokers were studied for four weeks, one week on their usual brand, two weeks on a low delivery cigarette and the final week back on their own cigarette (Forbes, Robinson, Hanley and Colburn, 1976). From butt analysis there was poor evidence of compensation although the subjects were allowed to select their own low delivery product which makes is difficult to draw firm conclusions.

C

As part of their studies using the puff recorder and puff duplicator, Creighton and Lewis (1978 a) studied cigarette switching. Smokers smoked a medium nicotine (1.4 mg) cigarette for one month, a high nicotine (1.8 mg) cigarette for the second month and the medium cigarette again for the third month. The estimated amount of nicotine that was delivered to the mouth of the smoker was assessed from ten laboratory sessions within each month. It was found that the level of nicotine delivered to the mouth stayed constant because subjects reduced their puffing intensity when they switched from medium delivery to high delivery cigarettes and increased their smoking intensity for the opposite switch from high cigarettes back to medium delivery products. However, subjects did not achieve mouth deliveries of 2.0 mg; men obtained 1.7 mg but women only achieved 1.0 mg in spite of their increased smoking intensity. Creighton and Lewis (1978 a) believe that this effect was due to cigarette construction ie, ventilation and longer apparent tip which inhibited smoking to the usual butt length. The clear conclusion was that smokers changed their smoking intensity in the direction of equalising nicotine deliveries. There was no evidence, in this study, that smokers modified the number smoked each day.

In another series of recordings of smoke generation, Adams (1976; 1978) measured puff number, puff volume and puff duration, as well as butt nicotine. He also found that smokers behaved differently on a low-medium nicotine (0.8 mg) cigarette in comparison with a medium delivery (1.4 mg) cigarette; they puffed harder on the lower delivery product and left a shorter butt. Butt nicotine analysis confirmed that more intense smoking resulted in proportionally more nicotine being taken into the mouths of smokers from the low nicotine than from the high nicotine cigarettes. A similar switching experiment (Rawbone, Murphy, Tate and Kane, 1978) studied smokers before and after they switched from their own medium delivery brand (average 1.22 mg of nicotine) to an undefined "low" delivery product. They found that subjects smoked harder on the lower delivery cigarette in comparison with their medium cigarette and compensated quite well (0.83 mg for low-medium against 0.96 mg for the medium delivery brands), as a result of increased puff volume. No increase in consumption was seen.

b. Partial Cigarette

In a partial cigarette study, Ashton and her colleagues (Ashton, Stepney and Thompson, 1978) tested subjects with two versions of their usual cigarettes throughout the study; a full length and a two-thirds length, which was calculated for each individual in the following manner. Subjects brought in the butts of their cigarettes, for a 24 hour period, and these were measured. The amount of the cigarette normally smoked was calculated and then a mark was made on the paper at two thirds of this length to indicate the amount of tobacco that they could smoke. The subjects were issued with the same number of marked cigarettes as they had smoked on the previous day and asked not to supplement them. In this way each smoker was deprived to the same degree but not by the same absolute amount. Comparative studies in the laboratory showed that subjects, given the two-thirds cigarettes, increased their puff duration and decreased their puff interval showing more intensive smoking of the reduced cigarette. However, the butt nicotine estimates showed that subjects did not compensate for the reduction sufficiently to obtain their usual amount of nicotine, as smokers had done in the study of Gritz et al (1976). The reason for this difference lies in the part of the cigarette that was smoked in the two studies. It is thought that about 61 per cent of nicotine in the smoke aerosol comes from the half of the cigarette nearer the filter, and only 39 per cent from the other half (Gritz et al, 1976) and so the subjects were not able to compensate sufficiently in the Ashton et al study.

c. Summary

These studies have examined the smoking intensity of low and high delivery brands by estimating the nicotine delivered to the mouth of the smokers from either the amount of nicotine that was deposited in the cigarette butt or puff duplication. The conservative conclusion from this body of data is that there are many different ways of smoking (machine deliveries being merely yields obtained from smoking to a standard set of parameters), and that subjects tend to smoke low delivery cigarettes more intensively and smoke high delivery brands

less intensively, even allowing for uncertainties of the filter tip analysis method (Creighton and Lewis, 1978 a).

It should be noted that although the filter tip analysis and puff duplication give an estimate of the amount of nicotine that is delivered to the mouth of the smoker, the value does not represent the effective dose because nicotine is not readily absorbed by the mouth from acidic smoke (see Section II A.1). Cigarette smoke must be inhaled for maximum absorption of nicotine. Of course over 90 per cent of smokers say that they usually inhale to some extent and 77 per cent say that they usually inhale "a lot" or "a fair amount" (Todd, 1972 TRC) so it is likely that a high percentage of the nicotine actually retained in the mouth is made available for absorption by the lungs, but accurate measures of the nicotine titration can only come from first estimating the amount of unwanted nicotine rejected from the mouth before inhalation (the "waste smoke") and then measuring inhalation itself.

3. Smoke Manipulation

Smoke manipulation particularly inhalation was apparently the most surprising aspect of the smoking habit for the Spaniards who first saw the American Indians smoking, but it is this manipulation which enables nicotine absorption. One index of manipulation is the amount of carbon monoxide exhaled after a cigarette. Carbon monoxide is absorbed into the bloodstream from the lungs and not in the mouth, so that increased carboxyhaemoglobin occurs only after inhalation. When the residual smoke has been expelled from the lungs, after a cigarette, carbon monoxide exchange from the blood to the lungs will occur so that the level of exhaled end-tidal carbon monoxide provides an index of uptake at the lungs and so enables comparisons of smoke manipulation.

a. Cigarette Switching

In a study referred to twice before, switching from smoking medium nicotine (1.4 mg) cigarettes to either high nicotine (3.2 mg) or low nicotine (0.3 mg) cigarettes was compared over a five hour work period by measuring exhaled carbon monoxide (Russell et al, 1973).

puffing titration had occurred. Urinary nicotine excretion on the high nicotine cigarette gave no support for titration when the machine delivery of 31 per cent higher than the usual brand was matched by urinary nicotine levels 30 per cent higher with the high nicotine cigarette than with the usual brand. However with the low nicotine cigarette, at 43 per cent of the usual cigarette the 24 hour excretion was 94 per cent. Altogether this study gives strong support for nicotine titration by smoke manipulation.

b. Partial Cigarettes

The experiment with half and three-quarter length cigarettes of Russell et al (1978) also included determinations of exhaled carbon monoxide and plasma nicotine. Although smokers used a greater number of the partial cigarettes, there was no evidence that they inhaled more carbon monoxide than would have been expected from the size of the cigarettes and the plasma nicotine was at the expected level as well, suggesting no titration. We will return to this contradictory result in the next sub-section.

c. Ventilated Holder

The results of the study on the ventilated holder (Sutton et al, 1978) which gave no support for titration in terms of the number smoked did provide some evidence for titration by smoke manipulation. A comparison of the observed 33 per cent reduction of carbon monoxide by the more ventilated holder at two days and seven days with the expected reduction of 52 per cent showed partial but significant compensation which was maintained throughout the test week. There seemed to be no compensation with the less ventilated holder which reduced carbon monoxide by 15 per cent. The outcome, in terms of plasma nicotine, was a reduction of only 40 per cent instead of the expected 58 per cent which confirms the effectiveness of smoke manipulation as a titration mechanism. This clear finding contrasted with the study of Russell et al (1978; Russell, 1980) in which partial cigarettes were smoked. Although smokers consumed more cigarettes in this study, their expired carbon monoxide and plasma nicotine levels were the same as those predicted if no titration had occurred. This study implies that smoke concentration is the cue for smoke manipulation because total

The problem of interpreting the results was the difference in carbon monoxide yields of the two cigarettes and the fact that the subjects slightly increased consumption of the low delivery and decreased the number of higher delivery cigarettes smoked. Exhaled carbon monoxide decreased for both switches and Russell has argued post hoc that the decrease with the high cigarettes represented less inhalation while the decrease with the low cigarettes was attributable to the lower carbon monoxide yield of that product. Plasma nicotine measures showed clear titration in half of the subjects when switched to the high nicotine cigarette while there was some evidence of titration for the group as a whole when switched to the low nicotine cigarette. When Ashton and Telford (1973) used unspecified high nicotine cigarettes and low nicotine cigarettes but with the same carbon monoxide delivery, the levels of exhaled carbon monoxide were inversely proportional to the nicotine deliveries of the cigarettes giving evidence of titration smoke manipulation.

Strong support for this conclusion was obtained from subjects who switched from a high nicotine (1.7 mg) cigarette with 17.2 mg of carbon monoxide to a low-medium nicotine (0.7 mg) cigarette with only 11.4 mg of carbon monoxide for five weeks (Guillerm and Radziszewski, 1974). Consumption increased slightly by three a day but carbon monoxide levels increased from 5.78 per cent to 7.43 per cent even though the machine estimated delivery of carbon monoxide from the low-medium nicotine cigarette was lower. In contrast, the shorter study of Turner et al (1974) found only slight evidence for compensation by smoke manipulation on the lower delivery brands.

More convincing evidence comes from an eleven week crossover study (Ashton, Stepney and Thompson, 1978) in which smokers switched from their usual medium (1.4 mg) nicotine brand to either high (1.84 mg) nicotine cigarettes ie an increase of 31 per cent in delivery or low-medium (0.6 mg) cigarettes ie a decrease of 57 per cent in delivery. The exhaled carbon monoxide levels showed an increase of only 10 per cent on the high nicotine cigarette, and were only 15 per cent lower on the low-medium cigarette. The plasma nicotine levels showed a similar pattern indicating that considerable post

smoke inhaled increased for smoke diluted by ventilation but not when the smoke concentration was the same as in the partial cigarettes (Russell, 1980).

d. Nicotine Preloading

As part of a series of studies on titration we administered an oral 1.0 mg dose of nicotine to smokers prior to smoking a low-medium nicotine (0.6 mg) cigarette (Wesnes, Pitkethley and Warburton, in preparation). The subjects were not told the true nature of the study and thought they were participating in a study of smoking and the effect of absorption of pure nicotine on hand tremor. Puffing behaviour, butt nicotine and exhaled carbon monoxide were measured. No differences were seen in puff duration and puff interval or the butt nicotine levels for the nicotine and placebo conditions. However, there was a significant reduction of exhaled carbon monoxide after the subjects had received a nicotine tablet indicating reduced smoke inhalation. Clearly the smokers were titrating their nicotine dose by smoke manipulation according to some internal mechanism sensitive to plasma nicotine levels.

e. Summary

Nicotine intake can be controlled by the amount of smoked inhaled as well as by cigarette consumption and by smoke generation. The amount of smoke inhaled depends on a combination of the quantity of waste smoke (the surplus expelled before inhalation) and the degree of inhalation. Rawbone et al (1978) compared exhaled carbon monoxide levels with smoke generation measures and found no correlation. Some smokers puffed relatively little but perhaps wasted little and inhaled the remaining smoke deeply, others puffed hard but perhaps wasted more and inhaled little. Thus, mechanisms are not necessarily interdependent. As far as nicotine absorption is concerned, inhalation is the final control on intake.

4. Conclusions

The experiments in this section were designed to investigate to what extent nicotine intake was controlled and the changes in smoking behaviour that enabled control. Taken together the studies show that nicotine intake is titrated to obtain more nicotine from lower delivery cigarettes and less nicotine from higher delivery brands. The methods of titration are number of units smoked, the length of cigarette smoked, the intensity of smoke generation, and the amount of smoke manipulation (waste smoke and inhalation). Unfortunately, most studies have only studied one of these titration mechanisms and found that some subjects do titrate, some titrate partially and some may not titrate at all using that particular method. Indeed it may be possible to titrate completely with some low delivery brands and the plasma nicotine levels in the studies of Russell support this assertion.

Evidence for control over the nicotine dose is important. It argues not only for nicotine being a necessary condition for smoking but also that smokers are trying to obtain a dose which will produce desired or needed pharmacological effects. Before considering the range of these pharmacological effects of nicotine it should be pointed out that the titration evidence suggests low delivery cigarettes will not necessarily be safer because they are oversmoked and tar exposure will increase to medium delivery levels while the carbon monoxide levels can exceed those of high delivery cigarettes (Ashton and Telford, 1973). Lowering deliveries can only be done effectively when we understand more fully the cues and mechanisms that smokers use to adjust their nicotine intake.

IV. NICOTINE PHARMACODYNAMICS

In this section we will discuss the actions of nicotine on the nervous system and on behaviour which may be used to account for the smoking habit. The literature is vast and so only illustrative experiments will be cited. In the first section the emphasis will be on the neurochemical changes that are produced by smoking doses of nicotine. In the second section the neurophysiological effects of nicotine will be outlined. In the third section these changes will be related to nicotine's effect on psychophysiological measures that have been associated with behaviour. The final, fourth section will discuss nicotine's action on human behaviour - the psychopharmacology of nicotine.

A. Neurochemical Action of Nicotine

Nicotine could modify neural transmission by interfering with one or more of the processes that are responsible for the regulation of transmitters ie (1) Alter transmitter synthesis by either changing the availability of transmitter precursors or changing the activity of the synthesising enzyme. (2) Interfere with the presynaptic storage of the transmitter. (3) Modify transmitter release into the synapse. (4) Alter the rate of transmitter inactivation by modifying the inactivating enzyme or the presynaptic reuptake (Warburton, 1975).

There is evidence in the literature from in vivo animal studies that nicotine produces changes in the brain levels of catecholamines, indoleamines and acetylcholine. The crucial questions are how can these changes in levels be related to the dynamics of transmitter systems and whether these changes can be extrapolated meaningfully to humans to explain the smoking habit.

A major problem, with the majority of these animal studies, is the unrealistically high dose levels of nicotine that have been tested. A 75 kg person, who takes between 0.75 and 3.0 mg of nicotine from a cigarette into his mouth, will receive a dose of between 10 and 40 µg per

kg. This figure is close to that derived by Armitage (1974) who calculated that the dose inhaled from each puff by a smoker is equivalent to an intravenous injection of 1 to 2 µg per kg. Assuming about 10 to 20 puffs per cigarette, this will give a dose of between 10-40 µg per kg per cigarette. There will obviously be differences because of the route of administration (inhalation and intravenous injection versus subcutaneous and intraperitoneal injection) and the different metabolic rates of different species, but it is probably safe to conclude that in mice, rats or cats, any dose which is over 10 times this dose (0.4 mg/kg) is well outside the "smoking" dose range.

1. Catecholamines

Studies on the catecholamines, dopamine and noradrenalin have been carried out by Lichtensteiger and his co-workers (Lichtensteiger, Felix, Lienhart and Hefti, 1976; Lichtensteiger, Richards and Koppe, 1978; Lichtensteiger, 1979) by Fuxe and his colleagues (Fuxe, Agnati, Eneroth, Gustafson, Hokfelt, Lofstrom, Skett and Skett, 1977; Eneroth, Fuxe, Gastafson, Hokfelt, Lofstrom, Skett and Agnati, 1977 a and b) and Westfall's laboratory (Westfall, Fleming, Fudger and Clark, 1967; Westfall, 1974).

These studies have given the same general picture in spite of wide differences in nicotine dose levels, which ranged from 0.33 mg/kg in one of Lichtensteiger's studies to four doses of 3 mg/kg at 30 min intervals in one of the experiments of Fuxe's group. Lichtensteiger reported that the fluorescence intensity of both dopamine and noradrenalin neurones was increased in the substantia nigra nuclei, zona compacta and zona incerta with doses of 0.33 mg/kg and 1.00 mg/kg of nicotine, suggesting increased activity in these neurones. This conclusion was supported by microelectrode recording of the neurones and biochemical analysis which showed some depletion of both transmitters. Westfall has also found that dopamine was reduced in the striatum of the mouse after 1 mg/kg of nicotine injected intraperitoneally.

Lichtensteiger also reported increased fluorescence of dopamine neurones in the rat median eminence of the diencephalon after 1 mg/kg

of nicotine and Westfall had previously found that this dose produced about 20 per cent depletion of noradrenalin in the same region in the mouse. Both of these findings would be consistent with increased neuronal activity in these catecholamine neurones and Lictensteiger demonstrated, with microelectrodes, that there was increased neural activity in this region as well as decreased growth hormone and prolactin secretion in the blood stream (dopamine is thought to be involved in the secretion of these hormones). There was also some evidence which was compatible with nicotine activating dopamine neurones controlling luteinizing hormone release.

Fuxe and his group investigated the specific relation between nicotine, catecholamines and gonadotrophin secretion. Unfortunately, they used large doses of 1 mg/kg, 2 mg/kg and 3 mg/kg injected four times in 90 mins before sacrifice and assay. Nicotine produced a depletion of 25 per cent in catecholamine levels in the median palisade zone of the median eminence of male rats (Fuxe et al, 1977) but hexamethonium prevented depletion. No changes were found in dopamine or noradrenalin receptor activity in in vitro studies so the changes are secondary to effects on cholinergic neurones. They also observed a reduction of luteinizing hormone and prolactin secretion in female rats. The implication of these findings for human smoking is dubious due to the very high doses that were used and it would be quite wrong to conclude from this data alone that nicotine could produce hormonal problems in pregnant and lactating women who smoked.

2. Indoleamines

Changes in the concentration and turnover of serotonin have been found after doses of nicotine. A dose of 1 mg/kg of nicotine, intraperitoneally injected into mice, markedly increased the levels of serotonin in the mesencephalon and diencephalon within 15 mins but not in the cortex (Essman, 1971). In the same study serotonin's major metabolite, 5-hydroxyindoleacetic acid, was also increased but there was a decreased serotonin turnover rate of 20 per cent and increased serotonin turnover time (+300 per cent). These data are not simple to interpret but clearly with this moderately large dose there are increased serotonin levels in some brain regions

Domino (1973) pointed out in a review of the behavioural studies, we must be cautious:- "The relevance of such large doses of nicotine given subcutaneously to the much smaller doses inhaled by man is certainly to be questioned" (P10).

The major effect with "smoking" doses has been to increase cortical release of acetylcholine but there is no evidence that release is due to a direct effect on the presynaptic release mechanisms of cortical neurones. One solution to the paradox lies in indirect activation of acetylcholine neurones which form part of the ascending cholinergic pathways to the cortex; this is discussed in the next section.

B. Neurophysiological Action of Nicotine

The action of many drugs has been explored by using the more readily accessible neurones in the peripheral nervous system which are more accessible than those in the central nervous system. Although caution must be exercised when using this data to explain central nervous system phenomena, in general, the principles that have been derived from such studies have proved useful in understanding the action of drugs on the brain. Thus the first studies will describe nicotine's action on these neural junctions.

1. Peripheral Nervous System

The action of nicotine on the nervous system has been known since the pioneering work of Dale who published a classic paper on acetylcholine "The action of certain esters and ethers of choline and their relation of muscarine" (Dale, 1914). This work established that nicotine mimicked the action of acetylcholine at autonomic ganglia and neuromuscular junctions and later it was established that acetylcholine was a transmitter at these synapses. Dale's work also revealed that some acetylcholine synapses, the post-ganglionic parasympathetic neurones, were better stimulated by muscarine than nicotine, and so it has become conventional to sub-divide peripheral nervous system neurones into "nicotinic" and "muscarinic" on the basis of their differential sensitivity to these two agonists - the two sorts of agonists that have been discovered. These neurones

probably due to increased synthesis and decreased release but, in spite of the decreased release, the large intraneuronal accumulation results in some leakage which elevates the level of 5-hydroxyindoleacetic acid. It is not clear whether the changes in serotonin after a moderately large dose of nicotine are important for human smoking.

3. Acetylcholine

Nicotine depletes whole brain acetylcholine in the rat (Pepeu, 1965) and mouse (Essman, 1971) in doses of 1 mg/kg. Depletion of transmitter could be a consequence of decreased synthesis, increased release from storage, increased release into the synaptic cleft or more effective enzymatic activation. There is no evidence that nicotine modifies acetylcholine synthesis (Hrdina, 1974) and the enzymatic inactivation of acetylcholine without any drug is extremely effective, which argues for a change in either storage of release. More importantly, there is strong evidence for increased free acetylcholine at the cortex after a "smoking" dose (40 µg/kg intravenously) in the cat (Armitage, Hall, Sellers, 1969) which is consistent with these two hypotheses.

The question of nicotine-induced changes in acetylcholine storage pools was tackled by Essman (1971). He found evidence of a decrease of acetylcholine in synaptic vesicles and in bound acetylcholine at the neocortex which suggests that acetylcholine was being released from storage by nicotine. However there was no increase in the free acetylcholine pool concentration which argues for increased release of the unbound transmitter and subsequent inactivation by acetylcholinesterase. The phenonemon of increased release at the cortex would be explained if nicotine enhanced presynaptic release mechanisms in cortical tissue but there is no in vitro evidence of enhancement (Hrdina, 1974). Thus we are left with the hypothesis that it is increased activity in the cholinergic neurones to the cortex which produces the in vivo depletion.

4. Conclusion

There is evidence that moderate to enormous doses of nicotine cause changes in catecholamines and indoleamines although the catecholamine changes were being mediated by cholinergic pathways. However, as

differ in the post-synaptic receptors as defined by Furchcott (1964):- "The specific molecular sites in (or on) the effector cell with which the molecules of a specific agonist must react in order to elicit the characteristic response of the cell to the agonist". In the case of nicotine the characteristic response is postsynaptic depolarization.

The effects of different doses of nicotine on cell membrane depolarization and subsequent action potentials were compared by Paton and Perry, (1953) using the cervical ganglion preparation of the cat. The drug was injected into the external carotid artery and all branches of the common carotid were blocked except the arterial branches supplying the ganglion itself, and the occipital artery to allow free blood flow past the ganglion. Then 0.2 ml of the solution containing 50 µg of nicotine tartrate was injected into the external carotid artery. This concentration is much larger than the 20-30 ng/ml found in the forearm vein after smoking (see Section II) but may be closer to the concentration ascending in the carotid artery after inhalation because none of this nicotine will have been metabolised. The effect of this dose was depolarization of the membrane and some reduction of the subsequent action potentials, a change which was similar to, but more transient than, the effects of a small dose of acetylcholine.

However 0.3 mg of nicotine, six times the above dose, produced prolonged depolarization and the action potentials were abolished ie ganglionic blocking. A challenge with a second dose of nicotine after the origianl depolarization, but before recovery of the action potentials, produced less depolarization than previously which demonstrated that nicotine was producing a competitive block of cholinergic receptors at very high doses. Exactly the same phenomenon has been observed with high doses of acetylcholine at the motor end-plate so that once again nicotine is mimicking acetylcholine. It has been suggested that the desensitization arises from the transformation of the acetylcholine receptor complex into an inactive form (Katz and Thesleff, 1957) and that the same effect occurs with nicotine. Whatever the reason, it seems unlikely that blood concentrations some 100,000 times that found in the human forearm vein ever occur in the smoker's brain and hence unlikely that a depolarization block occurs in brain neurones after nicotine. In summary, "smoking" doses of

nicotine precisely mimic acetylcholine and produce the same neural changes that would occur after natural activation of that synapse.

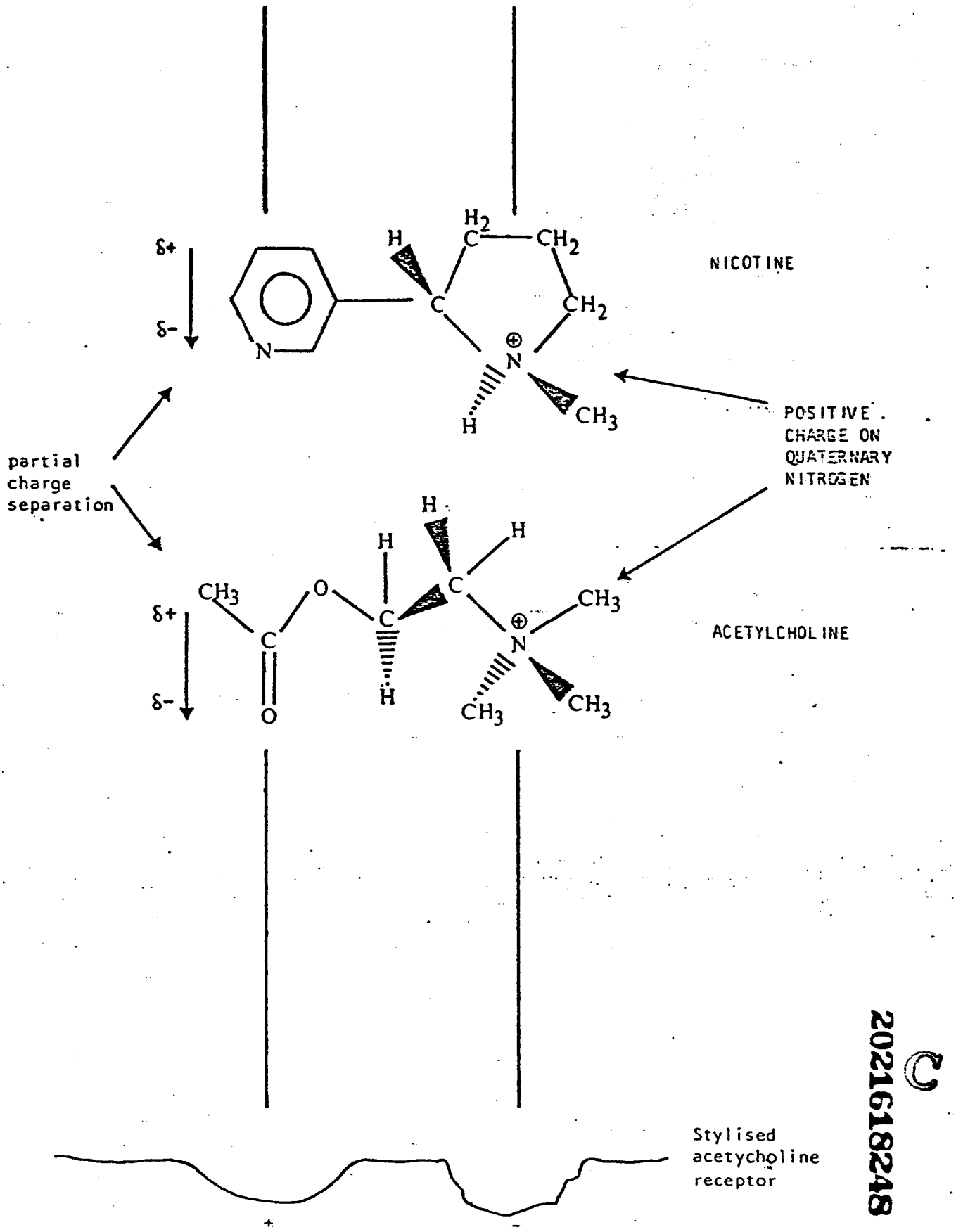
The reason for the exact mimicking of acetylcholine by nicotine at some cholinergic synapses is the remarkable similarity between the structures of the two molecules. Analysis by X-ray diffraction crystallography has shown that in order to interact with nicotine receptors, a molecule must consist of a planar acetoxy group or an aromatic ring separated from a methylated ammonium group which is about 130 picometres above the plane of the planar group (Pauling, 1970). Nicotine does consist of a planar pyridine ring perpendicular to the four coplanar atoms of the pyrollidine ring. Both nicotine and acetylcholine have a positively charged, methylated, tertiary nitrogen group ($N^{+}-CH_3$) in the pyrollidine ring which in nicotine is attached to an electronegative, isosteric nitrogen in the pyridine ring at just the distance to match the electronegative carbonyl oxygen of acetylcholine (see Figure 1).

2. Adrenal Medulla

One preganglionic nerve, the lesser splanchnic nerve, continues without synapses to the medulla of the adrenal gland. The adrenal medulla can be considered as an aggregation of specialised postganglionic cells which releases catecholamines into the bloodstream instead of releasing noradrenalin at its terminals onto other organs. Adrenalin is the major hormone that is released into the circulation to act on target cells while noradrenalin is mainly a neurotransmitter although the plasma levels can rise to concentrations which produce hormonal effects, for example, after heavy exercise.

Both catecholamines trigger haemodynamic effects; both raise blood pressure and dilate coronary vessels but adrenalin alone dilates skeletal muscle vessels. The rise in blood pressure is due to vasoconstriction of vessels of the skin, mucous membranes and viscera. The catecholamines have no direct effect on blood flow in the brain although an adrenalin solution of high concentration produces a sudden rise in systolic and diastolic pressure which can cause cerebral haemorrhage. The

NICOTINE AND ACETYLCHOLINE



These charges may be full or only partial

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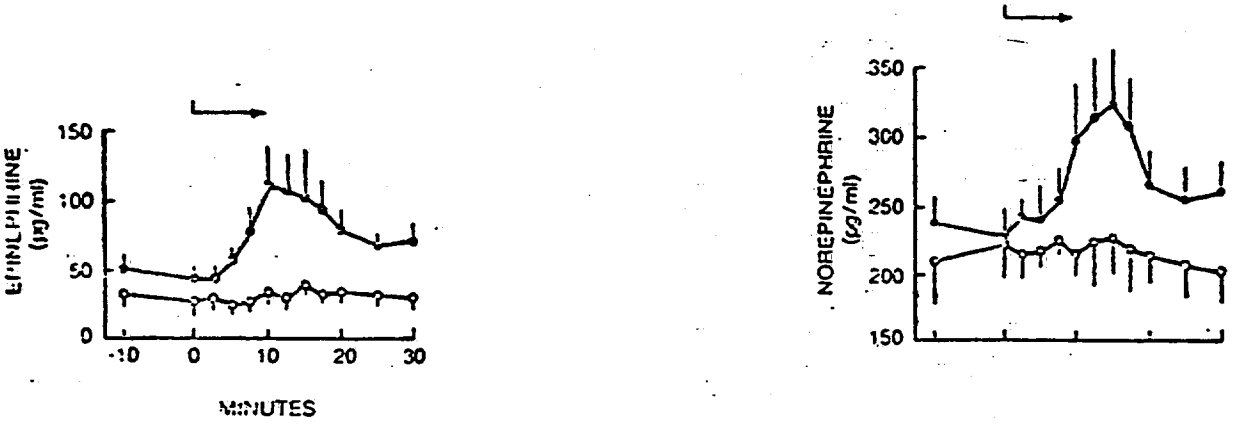
catecholamines have powerful effects on the heart increasing the shape of the pacemaker potential so that the firing threshold is reached more quickly and heart rate increases. It also increases the strength of heart rate contraction.

Of special interest are the metabolic effects of catecholamines. They accelerate delivery of glucose from the liver, reduce glucose clearance from the circulation and, as a consequence, the plasma levels of glucose rise. In addition the catecholamines stimulate lipolysis, increasing the delivery of free fatty acids to the liver. In the liver they may also act on hepatic metabolic processes to stimulate ketogenesis, which fuels those cells which do not depend on carbohydrates, and supplies glycerol for use in glucose synthesis. The increased free fatty acids will also reduce glucose uptake and use by cells with flexible metabolic requirements.

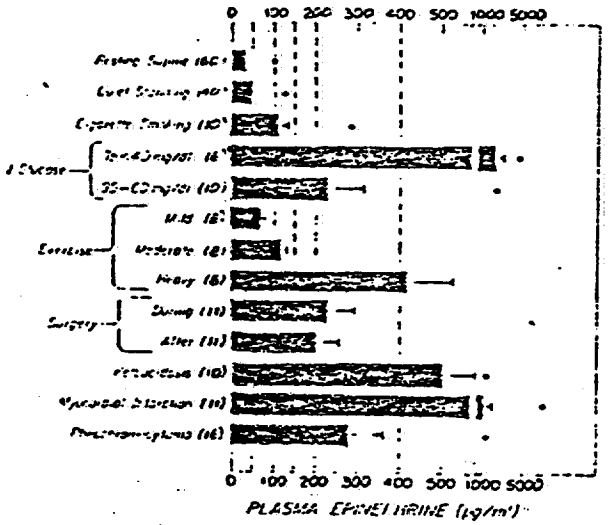
Classically these changes have been linked to the dramatic behaviour of flight or fight but the hormones have a much broader function. They are released when the person is anxious, concentrating hard, kissing or just changing from a lying down to sitting position; elevation of catecholamines does not necessarily indicate distress or unpleasant circumstances.

Smoking a single cigarette elevates both plasma noradrenalin and adrenalin within five minutes of starting the cigarette and they peak at, or soon after, the maximum plasma nicotine level is reached, see Figure 2 on page 39.

Figure 2

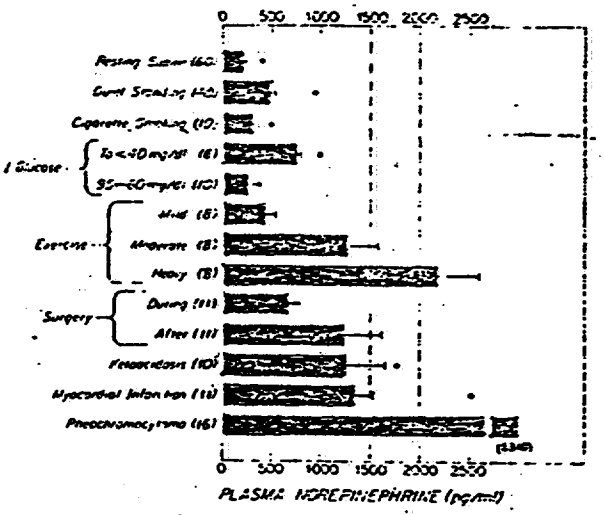


Mean (± S.E.) plasma norepinephrine and epinephrine concentrations in association with smoking (closed symbols) and sham smoking (open symbols). The arrows indicate the period of smoking (or sham smoking).



Venous Plasma Levels of Epinephrine in Human Beings in Various Physiologic and Pathophysiologic States (Mean ±S.E.M.).

Numbers in parentheses indicate the number of persons studied; solid circles represent the highest value observed. Dashed lines indicate the ranges of concentrations required to produce measurable changes in heart rate, systolic blood pressure, and blood glycerol (about 50 to 100 pg per milliliter), increases in plasma glucose, blood lactate, blood beta-hydroxybutyrate, and diastolic blood pressure (about 150 to 200 pg per milliliter), and initial decreases in plasma insulin (more than 400 pg per milliliter) in normal human subjects.[6]



Venous Plasma Levels of Norepinephrine in Various Physiologic and Pathophysiologic States in Human Beings (Mean ±S.E.M.).

Numbers in parentheses indicate the number of persons studied; solid circles represent the highest value observed. Dashed lines encompass the range of concentrations required to produce measurable metabolic and hemodynamic changes in normal subjects.[6]

The peak plasma concentration for noradrenalin is 330-350 pg/ml and for adrenalin it is 100-140 pg/ml (Cryer, Haymond, Santiago and Shah, 1976). These levels must be considered in the context of the levels for other activities (Cryer, 1980). It can be seen that cigarette smoking produces higher levels of noradrenalin than resting supine, but less than quiet standing and mild exercise and certainly less than moderate and vigorous exercise. A slightly different pattern is seen with adrenalin levels after smoking; they are about the same as after moderate exercise and greater than resting supine, quiet standing and mild exercise, but about a quarter of the levels seen after heavy exercise, over 400 pg/ml. Cryer (1980) has used graded infusions of noradrenalin and adrenalin to discover the threshold levels for haemodynamic and metabolic changes and found that smoking produces suprathreshold elevations of adrenalin but not noradrenalin. The adrenalin thresholds were 50-100 pg/ml for increased heart rate, 75-125 pg/ml for systolic pressor effects and lipolysis and 150-200 pg/ml for ketogenesis and glycolysis changes (see Figure 2).

In summary, nicotine, from a single cigarette, produces small increases in plasma catecholamines which just exceed the threshold for cardiovascular and some metabolic effects. It should be noted that "not only are noradrenalin and adrenalin rapidly cleared but they also accelerate their own metabolic clearance" (Cryer, 1980; P438) so that only very heavy smoking would produce accumulations of adrenalin and measurable metabolic effects. For example, in order to demonstrate that cigarette smoking could produce an increase in plasma free fatty acids and so contribute to coronary heart disease, atherogenesis, and atherosclerosis, Kershbaum and Bellet (1968) resorted to giving three cigarettes in 20 mins ie chain smoking. The lack of realism of this dose can be seen from the fact that if sleeping took up eight hours and three hours were spent eating (generous assumptions) then a 40 a day smoker would have a cigarette every 20 mins. For average smokers the effect of nicotine on the adrenal medulla is no more than taking moderate exercise. The fatigue alleviation that would result from the metabolic changes will be discussed at the end of the next sub-section on nicotine and the adrenal cortex.

3. Adrenal Cortex

The outer region of the adrenal gland is the adrenal cortex which contains zones of cells secreting hormones. The zona fasciculata and zona reticularies secrete the glucocorticoids of which the two most important, in humans, are cortisol and corticosterone. Unlike the adrenal medulla, release of hormones from the adrenal cortex into the circulation is controlled from the brain, via the release of adrenocorticotrophic hormone from the anterior pituitary, and not by the autonomic nervous system.

However the glucocorticoids like the catecholamines have marked metabolic effects but small or no haemodynamic action. They are essential for the mobilization of tissue proteins and for transferring the derived amino acids to the liver. The liver glycogen stores are limited and amino acids provide the major source of energy supply. In the liver, the glucocorticoids promote synthesis of enzymes that are used in gluconeogenesis. As well as conversion of amino acids to glucose, they also speed up extensive mobilization of depot lipid reserves, inhibit lipid synthesis and reduce glucose catabolism. Together these effects elevate plasma concentrations of glucose.

The glucocorticoids increase cardiac output and exert a "permissive action" on the cardiovascular effects of catecholamines in the sense that catecholamine vasoconstrictor responses are diminished when there are insufficient glucocorticoids. The two sets of hormones seem to be released in the same sort of circumstances, eg in response to stressors and when a person is concentrating. At the moment it is not clear what affects the different patterns of catecholamine and glucocorticoid release. Certainly, the two sets of hormones mobilize energy sources and prepare the person for action and reduce fatigue. The neural activation of the catecholamines ensures a rapid response, while the hormonal activation of the glucocorticoids results in a delayed, but more prolonged, action.

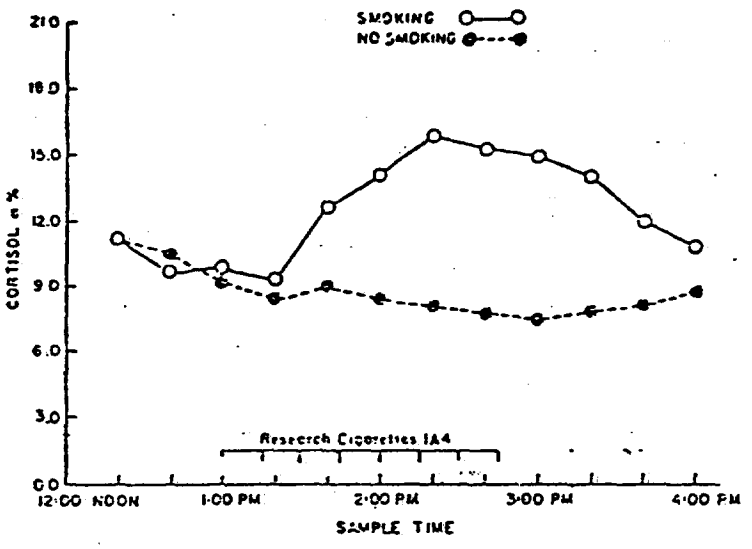
Adrenocortical secretion does increase after smoking although it does not seem to occur after only one cigarette. Kershbaum made habitual smokers chain smoke four unspecified cigarettes in thirty minutes and

took plasma samples at 30 mins and 90 mins (Kershbaum, Pappajohn, Bellet, Hirabayashi and Shafiiha, 1968). The plasma corticosteroid levels were markedly elevated after 30 mins and still above baseline at 90 mins. In the commentary Kershbaum mentions that there was some release (range 22 to 46 per cent) when "Two cigarettes were smoked by each of several subjects" but no further details were given.

In a second study, habitual smokers were given 8 high nicotine (2.5 mg) cigarettes to smoke in a two hour session (equivalent to over 100 cigarettes per day; Winternitz and Quillen, 1977). According to the authors "A sharp rise in plasma cortisol occurred after two cigarettes which was maintained through the 2nd hour and fell slowly after the smoking period" (P396). In fact their graph (Figure 3) shows that cortisol levels are the same or lower after the second cigarette and it is after the third cigarette in half an hour that cortisol had increased. Only continual smoking increased the plasma cortisol concentration and maintained it above baseline levels for the two hours. The best conclusion that can be drawn from these studies is that high nicotine doses from exaggerated smoking rates can elevate plasma glucocorticoids. An alternative interpretation is that the rapid smoking was aversive and stressed the subjects. Incidentally, the US Surgeon General's Report (1979) only cites the preliminary study of Winternitz and Quillen in which non-smokers smoked six cigarettes in two hours, were sick and had increased adrenocorticotrophic hormone levels.

If we accept the most charitable interpretation that smoking produces some release of glucocorticoids from the adrenal cortex then these hormones, combined with the catecholamine release, will make available energy sources for use by the brain and the rest of the body. In this way smoking would alleviate mental and muscle fatigue. Studies of carbohydrate and lipid use in physical work of different intensities have found that during exhausting work there was a depletion of carbohydrates, but subjective symptoms of fatigue disappeared within 15 min of ingesting glucose which increased the blood-sugar levels again (Christensen and Hansen, 1939). The central nervous sytem has low reserves of glucose and depends on blood carbohydrate for its supply of energy. In man about 60 per cent of the liver glucose output supplies brain metabolism, and so exhaustion

Figure 3



seems to be as much a central nervous phenomenon as is lack of sugar for muscles peripherally (Åstrand and Rodahl, 1970).

It has been suggested that the elevation of blood glucose could be responsible for the satisfaction derived from smoking because glucose would activate the reward pathways in the hypothalamus (Surgeon General, 1979). Carruthers (1975) used oxprenolol to block the responses to catecholamines release by smoking ie free fatty acid mobilization, blood pressure and heart rate increases. The subjective reports indicated no effect on satisfaction after smoking, which rules out the involvement of blood glucose (and blood pressure and heart rate increase) in satisfaction. It seems more likely that satisfaction is the outcome of the changes in the central nervous system.

4. Central Nervous System

The first evidence for "nicotinic" receptors in the central nervous system came from studies of the Renshaw cell in the spinal cord (Eccles, Eccles and Fatt, 1956). It was shown that when either 200 µg of acetylcholine or 1 µg of nicotine were injected close to the cell an action potential was produced. The response to nicotine was the same as that to acetylcholine but more prolonged because, unlike acetylcholine, it was not inactivated by acetylcholinesterase. When acetylcholinesterase was inhibited by physostigmine, acetylcholine produced a much larger response, but the response to nicotine was unchanged, which showed that nicotine's effect was directly on the post-synaptic receptors of the Renshaw cell and not via the release of acetylcholine. Nicotine antagonists reduced the response to both acetylcholine and nicotine, also indicating that nicotine was acting directly on cholinergic synapses. Many studies have now shown that there are nicotinic receptors on this cell although there seem to be muscarinic and even mixed synapses as well (Curtis and Ryall, 1966).

Studies with iontophoretically applied acetylcholine have revealed that this transmitter excites neurones in many regions of the brain (Phillis, 1970) including the medullary and mesencephalic reticular

formation, lateral and medial geniculate, caudate nucleus, ventrobasal complex of the thalamus, hippocampus, cerebellum, inferior colliculus and the Betz cells of the deep pyramidal layer of the cerebral cortex. Cortical cells and caudate nucleus cells clearly have muscarinic receptors which were relatively insensitive to nicotine while acetylcholine receptors in the geniculate nuclei, ventrobasal thalamus, hippocampus and reticular formation nuclei were sensitive to both nicotinic and muscarinic drugs. Cholinergic inhibitory neurones, with mixed nicotine and muscarinic receptors, have been found at the cortex in layers II, III and IV of the primary sensorimotor auditory and visual areas.

In spite of the clear evidence that the cholinergic neurones at the cortex are predominantly muscarinic, "smoking" doses of nicotine (eg 20 µg/kg in the cat) produce excitation of cortical cells (Knapp and Domino, 1962; Kawamura and Domino, 1969; Armitage, Hall and Sellers, 1969) and release of acetylcholine at the cortex (Armitage et al, 1969). In the study of Kawamura and Domino (1969) blood pressure was kept constant with drugs, so that the effect was not due to vascular changes.

Cortical acetylcholine release and cortical excitation can be produced by stimulation of the mesencephalic reticular formation and this phenomenon can be reduced in one hemisphere by unilateral destruction of this region ipsilaterally (Celesia and Jasper, 1966). In a neuropharmacological analysis of the effects of "smoking" doses of nicotine after destruction of the midbrain (Domino, 1967; Kawamura and Domino, 1969), 20 µg/kg of nicotine produced cortical desynchronization and hippocampal synchronization in cats with a caudal midbrain transection at the junction of the pons in exactly the same way as intact animals given nicotine. After bilateral lesions in the tegmental region of the midbrain, nicotine in doses up to five times the 20 µg/kg "smoking" dose did not activate the cortex. Clearly, nicotine's action on the cortex depends on an intact tegmental region. The ventral tegmental region of the mesencephalic reticular formation is the origin of a cholinergic pathway which projects to the cortex (Shute and Lewis, 1967) and there is good evidence that it terminates on the pyramidal Betz cells at the sensory cortex and produces electrocortical arousal (see review by Warburton, 1981).

The most parsimonious conclusion is that "smoking" doses of nicotine ascend in the carotid artery and excite nicotinic receptors on the tegmental-neocortical cholinergic pathway in the midbrain. Nicotine does not act directly on the cortex but the outcome of activation of the pathway at the midbrain is release of acetylcholine at the cortex and cortical desynchronization.

C. Nicotine and Human Psychophysiology

In this section we will consider the action of nicotine on the human cortex in the context of psychophysiology, the correlation of neurophysiological events with human behaviour. The first part will consider the effects of nicotine on cortical desynchronization, the second part will outline nicotine's action on the contingent negative variation while the third part will discuss event related potentials. The methodology of this research has been critically reviewed by Edwards (submitted for publication).

1. Cortical Desynchronization

Electrocortical activity is recorded by scalp electrodes which enable the measurement of the composite activity of cortical cells through the skull and scalp. When the firing of cells is synchronized, as they are during some periods of sleep, the electroencephalogram (EEG) shows low frequency (½ - 5 Hz), large amplitude (ie high voltage) waves (delta waves). When a person wakes and becomes alert, the waves decrease in amplitude and increase in frequency through theta waves (4 - 7 Hz), alpha waves (8-12 Hz) to beta waves (13 - 50 Hz). A high proportion of beta activity, cortical desynchronization, is correlated with a state of full alertness and concentration in the person while a high proportion of alpha activity is correlated with relaxed wakefulness.

Many human studies have shown that smoking increases the amount of cortical desynchronization in the form of an upward shift in dominant alpha frequency ie more 10 - 12 Hz (eg Hauser, Schwartz, Roth and Bickford, 1958), less total alpha activity and more beta activity (eg Knott, 1979; Murphree, 1979). Thus these human studies show that smoking

produces cortical desynchronization just as nicotine does in animal studies. In a study correlating performance with electrocortical activity, Warburton and Wesnes (1979) found that both cigarettes and nicotine-tablets increased the dominant alpha frequency (11.5 - 13.5 Hz) and beta activity (13.5 - 20 Hz).

In the same study, performance on a task involving concentration was improved by the same treatments. Many other studies at Reading University have confirmed that smoking and nicotine tablets, given to smokers and non-smokers, improve performance in tasks requiring sustained concentration (eg Wesnes and Warburton, 1978; 1982). In none of these studies were there differences in the effect of nicotine on performance in smokers and non-smokers. Therefore, it it significant that Murphree (1979) was unable to find any differences in the cortical desynchronization of smokers, who smoked at least 10 cigarettes per day, and non-smokers produced by an intravenous nicotine dose of 1.86 mg, a "smoking" dose. In other words, the smokers responded in the same way as non-smokers and there was no evidence of tolerance to nicotine's effect on electrocortical activity. These results make sense because of the molecular similarity of nicotine and acetylcholine. The brain cannot become tolerant to its own transmitters, and as nicotine is similar enough to acetylcholine, tolerance does not develop to nicotine either. This lack of tolerance to nicotine explains why smokers do not increase their consumption of cigarettes over the years (apart from compensating for any decrease in average nicotine - see page 90).

In concluding this illustrative review of nicotine's action on cortical desynchronization, it must be emphasised that the shifts produced by nicotine are within normal limits ie they are indistinguishable from those that occur when a person is concentrating hard. There is certainly no evidence of the EEG abnormalities that occur with other psychostimulants eg amphetamine. Smokers claim that they smoke to help them think and concentrate and nicotine's action on cortical desynchronization produces the neural state for satisfying this need. Evidence that smokers can control their nicotine intake to produce a specific brain state has come from contingent negative variation studies.

2. Contingent Negative Variation

The contingent negative variation (CNV) appears as a slow negative shift of cortical potential during the period between a warning signal and an imperative stimulus which requires a motor response or a decision. Thus, the CNV represents a cortical change associated with planned action before a response to a sequence of two or more events. Significant correlations have been reported between CNV amplitude and measures said to represent selective attention, arousal, motivation, anticipated energy output, conation, orientation, expectancy, and preparation for action, but selective attention or concentration is the most commonly used concept.

Experiments on the CNV and smoking (Ashton, Millman, Telford and Thompson, 1974; 1976; Ashton, Marsh, Millman, Rawlins, Telford and Thompson, 1978; Comer, Binnie, Burnett, Darby and Thornton, 1975; Binnie and Comer, 1978) have correlated CNV with subjective reports of feeling either "relaxed" or "stimulated" following smoking. Ashton collected personality information and estimated (by analysis of the cigarette butt) the amount of nicotine taken into each subject's mouth. After smoking, CNV amplitude increased in seven subjects, decreased in eleven and showed a biphasic response in four (Ashton et al, 1974). "Smoking" an unlit cigarette by three other subjects resulted in no CNV amplitude changes. Repetition of the smoking sessions for eleven of the subjects, on a different occasion, produced the same directional changes in the CNV in these individuals.

Ashton and her co-workers argue that the origin of the CNV is in the ascending reticular activating system and probably the limbic system and they assume that there is a positive relationship between CNV magnitude, activity in these systems and the individual's level of stimulation. Data from drug studies support these assumptions: CNV magnitude increased after doses of the psychostimulant caffeine and CNV magnitude decreased following oral doses of the sedative, diazepam (Valium) (Ashton et al, 1974; 1978).

Ashton et al related individual differences in CNV to personality and smoking behaviour. By dividing their group at the extraversion mean they

found that the eight more extraverted subjects took a smaller oral dose of nicotine per minute and showed a mean increase in CNV magnitude after smoking, while the eight more introverted subjects showed the reverse. They attempted to analyse subjective experiences of smoking but these did not provide clear data. However, there was some evidence from subjects that self-report of a "sedative" effect of smoking was associated with a fall in CNV whereas "stimulation" was associated with a rise in CNV.

Ashton and her co-workers (1978) also examined the effects of intravenous nicotine. They gave discrete pulses of nicotine to provide a total dose similar to that obtained by a smoker who inhales a cigarette delivering 1 - 2 mg of nicotine. The same direction of change in CNV occurred in individuals who took part in both smoking and nicotine sessions. Saline injections produced no significant changes. As a further refinement, Ashton et al (1978) examined the question of whether the CNV changes are dependent on the dose of nicotine or, alternatively, on the characteristics of the smoker and, therefore, largely independent of dose. Over a range of doses, from 12.5 - 800 µg, there was an inverted U relation between CNV magnitude and dose; with lower doses (12.5 - 50 µg) the CNV increased as the dose increased, but with further increases (100 - 800 µg) there was a progressive reduction in CNV magnitude. This pattern was evident for all seven subjects although the precise dose-response relation was not the same for each of them.

In summary, smoking and nicotine produced similar changes in the CNV in the same person. Nicotine increased or decreased the CNV amplitude depending on the dose and subjects seemed to control their smoking behaviour in order to obtain a particular dose. These findings were combined by Ashton to give the hypothesis that individuals adjust their smoking behaviour to the amount of nicotine for a particular brain state and so control their psychological state. The desired state will depend on the outcome of interaction between the individual and the situation and, by adjusting the nicotine dose, the same individual may use a cigarette to provide a stimulant effect on one occasion and a depressant effect on another.

3. Event-Related Potentials (ERP)

Event-Related Potentials, sometimes known as Averaged Evoked Potentials, are the complex electrical changes recorded at the same time as a physical or mental event and represent the activity of groups of neurones in the brain. The obvious advantage of the ERP technique is that it provides a continuous record of events occurring in the brain during psychological processes. The problem with recording the electrical activity from the scalp associated with a single event is that it is too small to detect against the background of cortical desynchronization and so "signal averaging" techniques are employed to distinguish ERP's from the obscuring background activity. If the ERP is the same with every event then it will become more and more recognizable against the random EEG noise during the averaging process.

With repetitive stimulation, the post-stimulus waveform between 0 to 250 msec consists of components which are essentially constant in amplitude, latency and scalp site distribution for a given stimulus. These exogenous components occur whether the subjects attend or not, are awake or asleep, aroused or relaxed. Of particular interest are the so-called endogenous components which are emitted or elicited, often in the absence of stimulation, and whose characteristics are partially independent of the physical characteristics of stimuli. The major endogenous component which has been identified is the P_3 or P300 whose latency ranges from 275 - 600 msec. The P300 is particularly sensitive to the subject's prior experience, intentions and decisions and varies according to the task requirements and experimental instructions.

A recent experiment (Edwards, Wesnes, Warburton and Gale, in preparation) enabled an analysis to be made of the effects of smoking on the ERPs to correct target detections in a rapid information processing task. In this test subjects were instructed to detect and respond to triplets of three odd or even digits in a sequence of single numbers that were presented on a TV screen at the rate of 100 per minute. Good performance depended on subjects maintaining their concentration throughout the 20 minute session. Preliminary analysis has shown that smoking produced large decreases in the latency of P300 (20-30 msec decrease) and small decreases in the amplitude of P300. A reduction in P300

latency is interpreted as a decrease in the time taken to evaluate or categorise a stimulus while a decrease in P300 amplitude is thought to mean that the subject is using less neural "resources" in processing. For example, when the probability of a signal is high then the amplitude is smaller than when the stimulus is novel because the information needs less analysis by the brain. Analysis of the performance showed that smoking increased the targets detected and decreased the reaction time (see sub-section IV D). This improvement of performance fits neatly with the P300 changes which are indicative of more efficient neural processing of the stimulus.

D. Psychopharmacology of Nicotine

In this section evidence will be presented on the implications for human behaviour of the neural states that are induced by nicotine. As we have seen, nicotine stimulates and produces increased neural efficiency. There is also evidence that nicotine can produce neural changes that have been interpreted as a sedation effect. Questionnaire surveys (eg McKennell, 1970; Thomas, 1973; Russell, Peto and Patel, 1974) have shown that a desire for stimulation and a desire for sedation are two of the major motives for smoking for a majority of smokers. Accordingly, this section will concentrate on the evidence for more efficient performance after nicotine and the effects of nicotine on mood states.

1. Performance

There are many possible tests of human performance which are sensitive to drugs, but a major problem is interpreting the data in terms of the psychological processes which are modified. These include (1) sensation (the input of information); (2) attention (selection of information); (3) processing of information; (4) learning and memory (storage of information); and (5) motor output (the response). Ideally, experiments are designed to study one process by minimising the influence of others on performance.

The earliest of the acceptable studies was done by Hull (1924). He used a within subject design and compared the effects on performance of tobacco smoke from a pipe and of moistened hot air. He measured several physiological variables and increases in heart rate indicated that subjects were absorbing nicotine from the tobacco smoke so it is reasonable to attribute the effects of smoking to nicotine. Nicotine improved reaction time and increased the speed but not accuracy of mental addition but impaired rote learning and memory span. In general, experienced smokers were more affected than non-smokers, suggesting that they had absorbed more nicotine from the tobacco smoke, probably by inhalation. This evidence suggests that nicotine is increasing information processing speed but interfering with information storage. However, it is not possible to rule out the explanation that the faster reaction was due to improved attention to the stimulus or the possibility that the impaired information storage was due to interference with the sensory input.

a. Sensation

There is little evidence from subjective reports of smokers that smoking has any effect on the ability to receive information from the environment, except perhaps for possible blunting of taste and smell. So it is not surprising that there is no confirmed evidence that nicotine significantly facilitates or impairs this process, although some research suggests that smoking raises sensory thresholds slightly ie the smokers are less sensitive to stimuli (Larson, Haag and Silvette, 1961). However, there are also reports that smoking doses of carbon monoxide increase brightness thresholds by about 3 per cent (Halperin, McFarland, Niven and Roughton, 1959) which would explain the small changes in threshold that were produced by smokers. Even for taste the evidence for changes after smoking are not clear cut. Pangborn and Trabue (1973) reviewed 16 experimental studies between 1937 and 1970 of which 11 reported impaired taste and/or smell with heavy smoking, and 5 which found no difference or negligible changes in sensitivity. The effects of nicotine alone on sensory thresholds have not been studied.